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# Virtual Histology of Cortical Thickness and Shared Neurobiology in 6 Psychiatric Disorders

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## **Virtual histology of cortical thickness reveals shared neurobiology underlying six psychiatric disorders**

Writing Committee for the Attention Deficit Hyperactivity Disorder, Autism Spectrum Disorder, Bipolar Disorder, Major Depressive Disorder, Obsessive Compulsive Disorder and Schizophrenia ENIGMA Working Groups

Word count = 3,467

### **Key Points**

Question: What are the neurobiological underpinnings of group differences in cortical thickness in various psychiatric disorders?

Findings: In this meta-analysis, regions of the cerebral cortex with greater expression of genes specific to pyramidal (CA1) cells are also regions with greater case-control group differences in cortical thickness in all six studied disorders, namely attention-deficit/hyperactivity disorder, autism spectrum disorder, bipolar disorder, major depressive disorder, obsessive-compulsive disorder and schizophrenia. There is a common profile of the group difference in cortical thickness shared amongst all these disorders (48% of the variance explained). A bioinformatics analysis of co-expression of genes associated with this shared profile suggests that these genes are involved in neurodevelopmental processes (prenatally), and processes underlying synaptic activity & plasticity (postnatally).

Meaning: There are shared neurobiological and cellular mechanisms underlying differences in cortical thickness across multiple psychiatric disorders - implicating a common role of prenatal development and postnatal functioning of the cerebral cortex.

**Abstract** (350 words maximum)

Importance: Large-scale neuroimaging studies have revealed group differences in cortical thickness across many psychiatric disorders. The underlying neurobiology behind these differences is not well understood.

Objective: To determine neurobiological correlates of group differences in cortical thickness between cases and controls in six disorders: attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), bipolar disorder (BD), major depressive disorder (MDD), obsessive-compulsive disorder (OCD) and schizophrenia (SCZ).

Design: Meta-analytic profiles of group differences in cortical thickness between cases and controls were generated using T1-weighted magnetic resonance images. Similarity between inter-regional profiles of cell-specific gene expression and those in the group differences in cortical thickness were investigated in each disorder. Next, principal component analysis was used to reveal a shared profile of group difference in thickness across the disorders. Gene co-expression, clustering and enrichment for genes associated with these disorders were conducted. Data analysis was conducted between June and December 2019.

Setting: A meta-analysis including 145 cohorts across 6 psychiatric disorders drawn from the ENIGMA Consortium.

Participants: The number of cases/controls in each of the six disorders were as follows: ADHD: 1,814/1,602; ASD: 1,748/1,770; BD: 1,547/3,405; MDD: 2,658/3,572; OCD: 2,266/2,007; and SCZ: 2,688/3,244.

Main outcomes and measures: Inter-regional profiles of group difference in cortical thickness between cases and controls.

Results: Inter-regional profiles of group differences in cortical thickness for each of the six psychiatric disorders were associated with profiles of gene expression specific to pyramidal (CA1) cells, astrocytes (except for BD) and microglia (except for OCD). Principal component analysis revealed a shared profile of difference in cortical thickness across the six disorders (48% variance explained); inter-regional profile of this principal component 1 was related to that of the pyramidal-cell gene expression. Co-expression analyses of these genes revealed two clusters: (1) a prenatal cluster enriched with genes involved in neurodevelopmental (axon guidance) processes; and (2) a post-natal cluster enriched with genes involved in synaptic activity & plasticity-related processes. These clusters were enriched with genes associated with all six psychiatric disorders.

Conclusion: There are shared neurobiological processes underlying differences in cortical thickness across multiple psychiatric disorders. These processes implicate a common role of prenatal development and postnatal functioning of the cerebral cortex in these disorders.

## Introduction

The advancement of large-scale magnetic resonance imaging (MRI) studies has enabled systematic investigations of cortical morphology, such as cortical thickness and surface area, across a variety of psychiatric disorders. In particular, the ENIGMA (Enhanced Neuroimaging Genetics Through Meta-Analysis) Consortium has conducted some of the largest MRI studies characterizing group differences between patients (cases) and controls in the cerebral cortex for a number of disorders, including attention deficit-hyperactivity disorder (ADHD),<sup>1</sup> autism spectrum disorder (ASD),<sup>2</sup> bipolar disorder (BD),<sup>3</sup> major depressive disorder (MDD),<sup>4</sup> obsessive-compulsive disorder (OCD),<sup>5</sup> and schizophrenia (SCZ).<sup>6</sup> Nonetheless, the neurobiology underlying these MRI-derived macroscopic features is not well understood.

As identified in *post-mortem* studies, there are subtle differences in the cellular composition of the cerebral cortex of patients diagnosed with various psychiatric disorders (vs. controls) such as the density of neurons and/or glial cells, and the extent of dendritic arborization.<sup>7</sup> Mostly lower neuronal density and/or neuronal size have been documented in ASD,<sup>8</sup> BD,<sup>9</sup> MDD,<sup>10,11</sup> OCD<sup>12</sup> and SCZ.<sup>13–15</sup> Similar alterations in the density of glial cells (astrocytes, microglia or oligodendrocytes) have been observed in ASD,<sup>8</sup> BD,<sup>9</sup> MDD,<sup>10,11</sup> and SCZ.<sup>16</sup>

Several MRI studies have demonstrated distinct inter-regional profiles of group differences in cortical thickness across the 34 regions of the Desikan-Killiany atlas.<sup>17</sup> We use the word ‘profile’ to refer to inter-regional (spatial) variations in a measure, such as cortical thickness, across the cerebral cortex. Lower cortical thickness in temporal regions in cases (vs. controls) is a common feature across ADHD, ASD, BD, MDD, OCD and SCZ<sup>1–6,18</sup>; a recent report of the ENIGMA cohorts showed cross-disorder correlations among disorders.<sup>19</sup> Likewise, large scale genome-wide association studies (GWAS) identify shared genetic architecture amongst these psychiatric disorders.<sup>20</sup>

No studies have investigated systematically the relationship between microscopic *ex-vivo* histology and macroscopic *in vivo* differences in cortical thickness across psychiatric disorders. This is required in order to facilitate our understanding of MRI-derived measures in a neurobiological context, as well as the usefulness of MRI for tracking of clinical progression of disorders and their treatment.

Here, we generate meta-analytic profiles of group differences in cortical thickness between cases and controls for ADHD, ASD, BD, MDD, OCD, and SCZ using an identical linear-modelling approach executed on each participating cohort. Next, we employ a virtual histology approach whereby inter-regional profiles of cell-specific gene expression are correlated - across the 34 cortical regions<sup>17</sup> - with inter-regional profiles of group differences in cortical thickness. Through a series of bioinformatic approaches, we then identify shared cellular correlates across the six psychiatric disorders.

## Methods

### Meta-analytic group differences in cortical thickness

T1-weighted MRI scans were acquired in 145 cohorts participating in the ENIGMA Consortium with varying MRI field-strength and vendors. Details regarding MRI acquisition and sample demographics are found in **eTable 1 and eTable 2**. FreeSurfer cortical reconstruction (several versions) was used to derive measures of cortical thickness in 34 regions (per hemisphere), as segmented using the Desikan-Killiany atlas.<sup>17,21</sup> Quality control was conducted by contributing cohorts, following standardized ENIGMA protocols (<http://enigma.ini.usc.edu/protocols/imaging-protocols/>). Individual ENIGMA groups performed multiple linear-regression analyses on their respective cohorts, which modelled cortical thickness of each region, separately, as a function of diagnosis (e.g., ADHD), age, age<sup>2</sup>, sex, and site-specific covariates (e.g., MR scanner). Individual cohorts obtained approval from local institutional ethics boards, and informed consent was obtained from study participants or their guardians. An inverse variance-weighted random-effects model from the “metafor” R package was used to generate meta-analytic profiles of group differences across the 34 regions for each disorder.<sup>22</sup> This report is a meta-analysis of shared data in the ENIGMA consortium rather than existing literature.

### MRI-derived similarity and genetic similarity

This analysis was carried out to evaluate similarity in pair-wise correlations in inter-regional profiles of group differences in cortical thickness and corresponding pair-wise correlations in genome-wide genetic architecture; described in eMethods. Group differences in cortical thickness were first correlated across psychiatric disorders with a biweight midcorrelation using R package WGCNA (rationale in eMethods).<sup>23</sup> Genetic correlations between psychiatric disorders were obtained from the Brainstorm consortium.<sup>20</sup> The similarity of the group differences in cortical thickness and genetic cross-disorder correlation matrices was tested for significance using Mantel's test from the “vegan” R package.<sup>24,25</sup>

### Virtual histology

Virtual histology is an approach that correlates – across space - an MRI-derived profile, such as an inter-regional profile of group differences in cortical thickness, with inter-regional profiles of cell-specific gene expression.<sup>26,27</sup> As described previously, gene-expression data from the Allen Human Brain Atlas (AHBA; 6 donors, 24 to 57 years of age) were first mapped to the 34 regions of the Desikan-Killiany atlas.<sup>28,29</sup> To ensure similarity of inter-regional profiles in gene expression across donors, and across the lifespan, we apply a conservative two-stage filtering process. First, a donor-to-median correlation in the AHBA was used to retain only genes whose profiles are consistent among the six donors (retaining 8,216 out of 20,737 genes present in AHBA). Second, the genes passing stage one are filtered based on inter-regional profile similarity with an independent atlas of gene expression, namely BrainSpan (retaining 2,511 out of 8,216 genes; see **eMethods** for additional details). The final set of 2,511 genes was used for

analyses conducted in this report. Next, single-cell RNA sequencing data from the mouse hippocampus and S1 cerebral cortex were used to categorize the 2,511 genes specific to nine cell types identified (CA1 pyramidal, S1 pyramidal, interneuron, astrocyte, microglia, oligodendrocyte, mural, endothelial and ependymal cells).<sup>30</sup> Pyramidal cell types (CA1 and S1) are labeled based on their anatomic origin. But the molecular characteristics of these pyramidal cells, as indexed by gene expression, are not restricted to the brain regions in which these two types of pyramidal cells were found. The use of these panels is analogous to a data reduction technique driven by neurobiologically relevant clustering (see **eMethods** for additional details). Inter-regional profiles of cell-specific gene expression were then correlated - across the 34 regions - with MRI-derived profiles to generate a distribution of correlation coefficients for each of the cell types. This distribution was then tested for significance using a resampling approach from 100,000 random samples. This analysis was restricted to MRI profiles from the left hemisphere only (due to data availability in AHBA).

### Co-expression analyses

Seed genes were defined by biweight midcorrelation between principal component 1 (PC1) profile (shared variance in group differences in cortical thickness across the six disorders) and cell-specific genes passing false discovery rate (FDR) corrected threshold  $p < 0.05$ .<sup>31</sup> For these analyses, we harmonized gene-expression data from human cerebral cortex across five datasets (AHBA,<sup>29</sup> BrainCloud,<sup>32</sup> Brain eQTL Almanac [Braineac],<sup>33</sup> Genotype Tissue Expression [GTEx],<sup>34</sup> and BrainSpan)<sup>35</sup>. The curation of these five gene-expression databases has been described previously and presented in eMethods.<sup>36,37</sup> In total there were 534 donors (ages 0 - 102 years old) with gene-expression data for 16,245 genes across all datasets. Co-expression analyses were generated using linear mixed-effects models where gene expression of each seed is modelled against other genes' expression with age and sex as fixed effects and donor identifier as a random effect. The top 0.1% of positively co-expressed genes for each of the seed genes were used to construct our co-expressed network panels.

### Gene trajectory clustering

Co-expressed genes were clustered based on their temporal pattern of gene expression using data from the BrainSpan atlas ([www.brainspan.org](http://www.brainspan.org)). This dataset was chosen for gene trajectory clustering as it is the only one that includes gene expression across prenatal and postnatal developmental periods (42 donors, age range from 8 post-conception weeks to 40 years of age; 11 cortical regions). Genes were clustered using mixed-effects models with nonparametric smoothing spline fitting available in the "TMixClust" R package (see eMethods for additional details).<sup>38</sup>

### Gene ontology, KEGG, and psychiatric disorder enrichment analysis

Gene ontology and KEGG pathway enrichment analysis were conducted using the R package "clusterProfiler".<sup>39</sup> GO (biological process ontology only) and KEGG terms with a minimum of 10 and a



maximum of 500 genes were included in the analysis. Redundancy of GO terms was removed based on similarity cut-off of 0.90. Enrichment between co-expressed genes and genes associated with psychiatric disorder were conducted using a hypergeometric test. Genetic variants associated with psychiatric disorder were derived from the DisGeNet database ([www.disgenet.org](http://www.disgenet.org)).<sup>40</sup> The background gene-set for all of the aforementioned enrichment test included 16,245 genes that were present in our harmonized dataset of gene expression for co-expression analyses. P-values were corrected using FDR procedure.<sup>41</sup>

## Results

**Meta-analysis** We characterized meta-analytic profiles of group differences in cortical thickness for each of the six disorders across the 34 regions of the cerebral cortex (**Figure 1**, **eTable 3-8**, **eFigure 1**, left hemisphere only). In total, there were 12,721 cases and more than 15,000 controls contributing to these profiles (**eTable 2**). Across the disorders, inter-regional variation in group differences of cortical thickness were positively correlated between SCZ and ADHD, ASD, BD, MDD & OCD (**Figure 2A**). Overall, there was a general trend of positive correlations ( $r_{\text{bicor}} > 0$ ) of group differences across all six psychiatric disorders (**Figure 2A**). Genetic correlations, as quantified by linkage-disequilibrium score regression, also showed a number of pair-wise positive correlations among these psychiatric disorders, in particular for SCZ (**Figure 2B**, reproduced using data from the Brainstorm consortium).<sup>20</sup> Cross-disorder similarity of differences in cortical thickness (derived from MRI, **Figure 2A**) was correlated positively with cross-disorder genetic similarity (derived from GWAS, **Figure 2B**), explaining 27% of variance (Mantel's p value = 0.034, Pearson p value = 0.045).

**Virtual histology of group difference in cortical thickness** Inter-regional variation in the expression of genes specific to pyramidal (CA1) cells correlated negatively with the inter-regional profile of group differences in cortical thickness in each of the six psychiatric disorders ( $-0.08 > r > -0.23$ , FDR-p-value < 0.05, **Figure 3**, **eTable 9**, **eFigure 2**). Thus, regions with greater expression of pyramidal (CA1) specific genes showed greater differences in cortical thickness between cases and controls. We also observed this negative relationship with inter-regional profiles of expression of genes specific to astrocytes and microglia in all six disorders except BD (no correlation with astrocytes) and OCD (no correlation with microglia). Lastly, we observed a negative relationship between pyramidal (S1) specific expression and group differences in thickness in BD only.

**Principal component analysis** Given the similarity of findings across the six disorders vis-à-vis virtual histology, we used principal component analysis to reduce the dimensions of the data (**Figure 4A**). The first principal component (PC1) explained 48% of variation in group differences of thickness profiles across the six disorders (**eFigure 3**). PC1 was positively correlated with each of disorder's profiles (**eFigure 3C**), and its inter-regional profile was negatively associated with the inter-regional profiles of pyramidal- (CA1), astrocyte-, and microglia-specific gene expression (**Figure 4B**); regions with greater

expression of cell-specific genes showed greater differences in cortical thickness between cases and controls.

Shared neurobiology across disorders To investigate the relationship between PC1 and CA1 pyramidal specific genes, we used all CA1 genes associated significantly (FDR  $p < 0.05$ ) with PC1 as seed genes for co-expression analyses. Data from the AHBA, BrainEAC, BrainSpan, BrainCloud, and GTEx were harmonized to identify robust co-expression associations across the genome (**eFigure 4&5**). These “PC1-CA1” co-expressed genes ( $n = 412$  genes) were clustered based on their temporal pattern of expression using unsupervised nonparametric mixed modelling. This analysis yielded two clusters: Cluster 1 was upregulated during prenatal time periods and down regulated in postnatal life; and Cluster 2 that showed the opposite developmental trajectory (**Figure 5A**). GO enrichment analysis revealed involvement of neurodevelopmental processes (axon development; FDR-pvalue= $5.15E-05$ ) in the “prenatal” cluster (**Figure 5B**, **eFigure 6**) and involvement of synaptic signalling/neurotransmission and synaptic plasticity related terms (FDR-pvalue= $5.11E-09$ , and  $2.31E-03$ , respectively) in the “postnatal” cluster (**Figure 5C**, **eFigure 6**). Gene-enrichment analysis showed that the prenatal cluster is enriched in genes associated with ASD, BD, MDD and SCZ, while the postnatal cluster is enriched only in genes associated with ADHD and SCZ (FDR-pvalue  $< 0.05$ , **eFigure 7**). The entire co-expressed network (i.e., genes from both clusters) is enriched for all six disorders, at varying levels of enrichment (**eFigure 7**). Finally, with the aid of laminar gene-expression data from the developing human neocortex, we show that the prenatal cluster was upregulated in the cortical subplate zone and cortical plate (AUROC= $0.68$ , FDR-pvalue =  $2.35E-15$ ), while down-regulated in the ventricular zone (AUROC= $0.30$ , FDR-pvalue =  $1.30E-17$ ; **eFigure 8**; **eTable 10**). This held true for the post-natal cluster as well (**eFigure 8**, **eTable 11**).

The analysis described above was repeated for the astrocyte- and microglial-specific genes. PC1-Astrocyte co-expressed genes ( $n = 168$  genes) were enriched in metabolic processes such as amino acid transport (FDR-p-value= $2.09E-03$ ), as well as enriched in genetic variants associated with BD and SCZ (FDR-p-value= $0.013$  &  $0.014$ , respectively, **eFigure 9**). PC1-Microglia co-expressed genes ( $n = 118$  genes) were enriched in immune-related processes (FDR-p-value= $1.7E-08$ ) and showed no enrichment with genetic variants associated with any of the six psychiatric disorders (**eFigure 10**).

## Discussion

We characterized robust inter-regional differences in cortical thickness between cases and controls across the cerebral cortex in six common psychiatric disorders, as done previously by the individual Working Groups of the ENIGMA Consortium.<sup>1–6,18</sup> The inter-regional profiles presented in this report were generated using the same linear model (with the same covariates) in each of the 145 participating cohorts and – as such – allow for direct comparisons of these profiles across the six disorders. This also facilitated our observation of the similarity between shared differences in MRI-derived thickness and

genetic architecture across these six disorders, an observation suggesting the presence of genetic variants that may be associated with “vulnerable” brain phenotypes in common for the six disorders investigated here (**Figure 2**).

Virtual histology identified common cell-specific associations between *ex vivo* gene expression and *in vivo* MRI-derived group differences in cortical thickness across the 34 cortical regions. In this analysis, all six disorders showed a negative association with expression profiles specific to CA1 pyramidal cells. Regions with greater group differences in cortical thickness are the regions with greater expression of pyramidal (CA1-like) specific genes within the “normative” human brain – potentially indicating vulnerability of these regions. Although the CA1 pyramidal-cell panel is labelled based on the source of these cells (CA1 region of the hippocampus), this does not mean that biological processes implicated in “CA1” genes are restricted to this region; in fact, similar molecular processes are present throughout the human cerebral cortex (see Supplement for additional details). As such, we interpret the functional relevance of these genes being related to differences in cortical thickness. It is important to state that the gene expression used throughout this report comes from individuals without any diagnoses of neurological or psychiatric disorders. Studies linking cell-specific genes with psychiatric GWAS-associated genes show similar enrichment of CA1 pyramidal cells in ASD, BD, MDD, and SCZ.<sup>42</sup> This is another line of evidence linking genetically identified enrichment of CA1 pyramidal cells (previous study<sup>42</sup>) with MRI identified enrichment of CA1 pyramidal cells within psychiatric disorders (this report).

Principal component analysis identified a common component of these cortical differences, indicating a shared inter-regional profile of case-control differences in cortical thickness among all six disorders. Although not the primary focus of this report, we also report other PCs (explaining less variance); these appear to capture mostly disease-specific variations in group differences in cortical thickness (see **eFigure 3** for more details). As expected from the disease-specific analyses, this PC1 profile was associated with the same three cell types, namely CA1 pyramidal, astrocyte, and microglia. The CA1 pyramidal geneset is enriched with biological processes related to dendritic arborization<sup>27</sup>, and extensive dendritic branching is a key morphological phenotype of pyramidal neurons.<sup>43</sup> Similarly, our phenotype is derived from cortical thickness, a measure that is directly correlated with ex-vivo dendrite length across individuals ( $R^2=0.25$ ).<sup>44</sup> Dendrites control the flow and integration of information within neurons and are a medium of structural plasticity within the cerebral cortex. Remodeling of dendritic trees and dendritic spines have been observed as a result of environmental (stress, sensory enrichment/deprivation) and genetic influences acting both early and later in life.<sup>45,46</sup> Alterations in dendritic morphology, such as reduction in size of dendritic arborization, have been described in *post mortem* samples from the cerebral cortex of patients with ASD<sup>47,48</sup>, BD<sup>49</sup>, SCZ<sup>49</sup>, depression<sup>50</sup>, and anxiety.<sup>50</sup>

The network of genes co-expressed with the (CA1) pyramidal genes associated with PC1 contained two clusters: one upregulated during the prenatal and the other during the postnatal period. Through a series of bioinformatic approaches we found evidence for two sets of processes involving cortical development and cortical functioning and, based on the temporal profile, the influence of these processes prevails during prenatal (prenatal cluster) and postnatal (postnatal cluster) life, respectively. The emergence of these two clusters is highly convergent with the two-hit hypothesis regarding the etiology psychiatric disorders, particularly with schizophrenia.<sup>51</sup> We speculate that the group differences in cortical thickness observed across the six psychiatric disorders are a summation of processes occurring throughout life (pre- and postnatal) whereby atypical development and/or impaired cortical functioning leave a morphological signature in the cerebral cortex.

#### Prenatal/neurodevelopmental features of psychiatric disorders

The development of the cerebral cortex during gestation is a complex process with a high susceptibility to perturbations. It is hypothesized that the risk for psychiatric disorders increases due to perturbations in normal neurodevelopment.<sup>52,53</sup> Cross-disorder GWAS studies of ADHD, affective disorder, anorexia, ASD, BD, and SCZ have all implicated genes involved in regulating neurodevelopmental processes within radial glia and interneurons of the developing neocortex.<sup>54</sup>

The prenatal (co-expression) cluster was enriched in neurodevelopmental processes such as axonogenesis/guidance, dendrite development, and - in general terms - neuron projection guidance. Axon guidance was also one of the key GO terms found in the aforementioned cross-disorder GWAS study.<sup>54</sup> Axon guidance is a process that directs growth cones as to establish the correct neuron pathways and cortical circuits. The strongest evidence in implicating axon-guidance proteins in psychiatric disorders is found in ASD whereby expression and GWAS studies converge on canonical axon guidance proteins such as Slits, Robos, and Semaphorins, all of which are present in our PC1-CA1 co-expressed genes (**eFigure 11**).<sup>55</sup> See supplemental discussion regarding subplate enrichment. We speculate that early changes in neurodevelopmental processes may render certain regions and cell types (pyramidal cells and their dendrites) more vulnerable and, as such, more likely to be involved in the etiology of all psychiatric disorders. This may explain the shared profile of difference we observe.

#### Postnatal/functional features of psychiatric disorders

There is strong genetic, molecular and histological evidence demonstrating synaptic dysfunction and pathological changes in spine density and morphology in psychiatric disorders (particularly ASD, SCZ, MDD, and BD).<sup>56–59</sup> Alterations in these processes are likely to influence structural plasticity and subsequent formation of complex and adaptable circuits. Both genetic and experience-dependent factors play a role in structural plasticity across life, and a summation of these factors may increase or decrease the risk of developing a psychiatric disorder. These structural (dendritic spine) changes are prominent

during periods of maturation (childhood and youth) – coinciding with the peak age in incidence of psychiatric disorders.<sup>56,60</sup> The postnatal cluster of co-expressed genes was enriched in synaptic transmission, and regulation of synaptic plasticity. We hypothesize that this cluster of genes is indicative of plasticity-related morphological changes in the cerebral cortex that may – in part – reflect adverse experiences common across all psychiatric disorders. This interpretation is consistent with the fact that there are fewer disorder-associated gene variants enriched in the postnatal cluster as compared with the prenatal cluster, potentially indicating that the postnatal processes are related to environmental rather than genetic components of risk for psychiatric disorders.

### Limitations

There are several limitations to the approach used in this report. First, only 2,511 genes determined as having ‘representative’ inter-regional profiles of their expression are used for virtual histology. We chose this conservative approach given that inter-regional profiles in case-control differences and those in gene expression come from two different sets of brains (see Supplement for additional details). This limitation may lower our ability to capture other relevant neurobiological signals. In an attempt to mitigate this limitation, downstream analyses use co-expression to broaden the scope of the genes investigated, albeit indirectly. Secondly, we are using single-cell data from mice, which have shown general conservation with human data. There are, however, some species-specific differences that may not be accounted for in this report (see **eMethods** for details on single-**cell** vs. single-**nucleus** dataset).<sup>61</sup> Thirdly, our analysis uses a relatively coarse parcellation allowing us to capture gross inter-regional patterns of group differences in cortical thickness. This might, however, increase the potential for false positives (reduced number of comparisons) and for missing subtle (vertex-level) variations. Lastly, when interpreting T1-weighted MRI, we assume that these estimates reflect true variations in brain phenotype rather than measurement error, artifacts, or other physiological sources of T1 signal.

### Conclusion

In summary, we characterized shared neurobiology across six psychiatric disorders that implicates pyramidal cells (and dendrites) in representing a possible target of perturbations that may increase a general vulnerability to mental illness. Our bioinformatics-based analyses point towards involvement of neurodevelopmental (prenatal) and plasticity-related (postnatal) aspects underlying pathophysiology of psychiatric disorders and their brain correlates. These shared aspects of psychiatric disorders highlight the importance of transdiagnostic approaches in psychiatry.

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*Writing Committee for the Attention Deficit Hyperactivity Disorder, Autism Spectrum Disorder, Bipolar Disorder, Major Depressive Disorder, Obsessive Compulsive Disorder and Schizophrenia ENIGMA Working Groups*

Yash Patel, BHSc<sup>1,2</sup>, Nadine Parker, MSc<sup>1,2</sup>, Jean Shin, PhD<sup>3</sup>, Derek Howard, MSc<sup>4</sup>, Leon French, PhD<sup>4</sup>, Sophia I. Thomopoulos, BA<sup>5</sup>, Elena Pozzi, PhD<sup>6</sup>, Yoshinari Abe, MD, PhD<sup>7</sup>, Christoph Abé, PhD<sup>8</sup>, Alan Anticevic, PhD<sup>9</sup>, Martin Alda, MD<sup>10</sup>, Andre Aleman, PhD<sup>11</sup>, Clara Alloza, PhD<sup>12</sup>, Silvia Alonso-Lana, PhD<sup>13</sup>, Stephanie H. Ameis, MD, MSc<sup>14</sup>, Evdokia Anagnostou, MD<sup>15</sup>, Andrew A. McIntosh, MD<sup>16</sup>, Celso Arango, MD, PhD<sup>17</sup>, Paul D. Arnold, MD, PhD<sup>18</sup>, Philip Asherson, MBBS, PhD<sup>19</sup>, Francesca Assogna, PhD<sup>20</sup>, Guillaume Auzias, PhD<sup>21</sup>, Rosa Ayesa-Arriola, PhD<sup>22</sup>, Geor Bakker, PhD<sup>23</sup>, Nerisa Banaj, PhD<sup>20</sup>, Tobias Banaschewski, MD, PhD<sup>24</sup>, Cibele E. Bandeira, MSc<sup>25</sup>, Alexandr Baranov, MD, PhD<sup>26</sup>, Núria Bargalló, MD, PhD<sup>27</sup>, Claiton HD. Bau, PhD<sup>25</sup>, Sarah Baumeister, PhD<sup>24</sup>, Bernhard T. Baune, MD, PhD<sup>28</sup>, Mark A. Bellgrove, PhD<sup>29</sup>, Francesco Benedetti, MD<sup>30</sup>, Alessandro Bertolino, MD, PhD<sup>31</sup>, Premika S W. Boedhoe, PhD<sup>32</sup>, Marco Boks, MD, PhD<sup>33</sup>, Irene Bollettini, PhD<sup>30</sup>, Caterina del Mar Bonnin, PhD<sup>34</sup>, Tiana Borgers, MSc<sup>28</sup>, Stefan Borgwardt, MD<sup>35</sup>, Daniel Brandeis, PhD<sup>24</sup>, Brian P. Brennan, MD<sup>36</sup>, Jason M. Bruggemann, PhD<sup>37</sup>, Robin Bülow, MD<sup>38</sup>, Geraldo F. Busatto, MD, PhD<sup>39</sup>, Sara Calderoni, MD, PhD<sup>40</sup>, Vince D. Calhoun, PhD<sup>41</sup>, Rosa Calvo, MD, PhD<sup>42</sup>, Erick J. Canales-Rodríguez, PhD<sup>13</sup>, Dara M. Cannon, PhD<sup>43</sup>, Vaughan J. Carr, MD<sup>44</sup>, Nicola Cascella, MD<sup>45</sup>, Mara Cercignani, PhD<sup>46</sup>, Tiffany M. Chaim-Avancini, MD, PhD<sup>39</sup>, Anastasia Christakou, PhD<sup>47</sup>, David Coghill, MD<sup>48</sup>, Annette Conzelmann, PhD<sup>49</sup>, Benedicto Crespo-Facorro, MD, PhD<sup>50</sup>, Ana I. Cubillo, PhD<sup>51</sup>, Kathryn R. Cullen, MD<sup>52</sup>, Renata B. Cupertino, PhD<sup>25</sup>, Eileen Daly, PhD<sup>53</sup>, Udo Dannlowski, MD, PhD<sup>28</sup>, Christopher G. Davey, MBBS(Hons), PhD<sup>54</sup>, Damiaan Denys, MD, PhD<sup>55</sup>, Christine Deruelle, PhD<sup>21</sup>, Annabella Di Giorgio, MD, PhD<sup>56</sup>, Erin W. Dickie, PhD<sup>57</sup>, Danai Dima, PhD<sup>58</sup>, Katharina Dohm, PhD<sup>28</sup>, Stefan Ehrlich, MD, PhD<sup>59</sup>, Benjamin Ely, PhD<sup>60</sup>, Tracy Erwin-Grabner, PsyD, MA<sup>61</sup>, Thomas Ethofer, MD<sup>62</sup>, Damien A. Fair, PA-C, PhD<sup>63</sup>, Andreas J. Fallgatter, MD<sup>62</sup>, Stephen V. Faraone, PhD<sup>64</sup>, Mar Fatjó-Vilas, PhD<sup>13</sup>, Jennifer M. Fedor, BS<sup>65</sup>, Kate D. Fitzgerald, MD<sup>66</sup>, Judith M. Ford, PhD<sup>67</sup>, Thomas Frodl, MD, PhD<sup>68</sup>, Cynthia HY. Fu, MD, PhD<sup>69</sup>, Janice M. Fullerton, PhD<sup>70</sup>, Matt C. Gabel, PhD<sup>71</sup>, David C. Glahn, PhD<sup>72</sup>, Gloria Roberts, PhD<sup>73</sup>, Tinatin Gogberashvili, PhD<sup>74</sup>, Jose M. Goikolea, MD, PhD<sup>34</sup>, Ian H. Gotlib, PhD<sup>75</sup>, Roberto Goya-Maldonado, MD<sup>61</sup>, Hans J. Grabe, MD<sup>76</sup>, Melissa J. Green, PhD<sup>44</sup>, Eugenio H. Grevet, MD, PhD<sup>77</sup>, Nynke A. Groenewold, PhD<sup>78</sup>, Dominik Grotegerd, PhD<sup>28</sup>, Oliver Gruber, MD<sup>79</sup>, Patricia Gruner, PhD<sup>9</sup>, Amalia Guerrero-Pedraza, MD, PhD<sup>80</sup>, Raquel E. Gur, MD, PhD<sup>81</sup>, Ruben C. Gur, PhD<sup>81</sup>, Shlomi Haar, PhD<sup>82</sup>, Bartholomeus CM. Haarman, MD, PhD<sup>83</sup>, Jan Haavik, MD, PhD<sup>84</sup>, Tim Hahn, PhD<sup>28</sup>, Tomas Hajek, MD, PhD<sup>10</sup>, Benjamin J. Harrison, PhD<sup>85</sup>, Neil A. Harrison, MD, PhD<sup>46</sup>, Catharina A. Hartman, PhD<sup>86</sup>, Heather C. Whalley, PhD<sup>16</sup>, Dirk J. Heslenfeld, PhD<sup>87</sup>, Derrek P. Hibar, PhD<sup>88</sup>, Eva Hilland, PhD<sup>89</sup>, Yoshiyuki Hirano, PhD<sup>90</sup>, Tiffany C. Ho, PhD<sup>91</sup>, Pieter J. Hoekstra, MD, PhD<sup>92</sup>, Liesbeth Hoekstra, MD<sup>93</sup>, Sarah Hohmann, MD, PhD<sup>24</sup>, L. E. Hong, MD<sup>94</sup>, Cyril Höschl, MD, DrSc, FRCPsych<sup>95</sup>, Marie F. Høvik, MD<sup>96</sup>, Fleur M. Howells, PhD<sup>97</sup>, Igor Nenadic, MD<sup>98</sup>, Maria Jalbrzikowski, PhD<sup>99</sup>, Anthony C. James, MD, MPhil<sup>100</sup>, Joost Janssen, PhD<sup>12</sup>, Fern Jaspers-Fayer, PhD<sup>101</sup>, Jian Xu, PhD<sup>102</sup>, Rune Jonassen, PhD<sup>89</sup>, Georgii Karkashadze, PhD<sup>103</sup>, Joseph A. King, PhD<sup>59</sup>, Tilo Kircher, MD, PhD<sup>104</sup>, Matthias Kirschner, MD<sup>105</sup>, Kathrin Koch, PhD<sup>106</sup>, Peter Kochunov, PhD<sup>94</sup>, Gregor Kohls, PhD<sup>107</sup>, Kerstin Konrad, PhD<sup>108</sup>, Bernd Krämer, PhD<sup>79</sup>, Axel Krug, PhD<sup>104</sup>, Jonna Kuntsi, PhD<sup>19</sup>, Jun Soo Kwon, MD, PhD<sup>109</sup>, Mikael Landén, MD, PhD<sup>110</sup>, Nils I. Landrø, PhD<sup>89</sup>, Luisa Lázaro, MD, PhD<sup>42</sup>, Irina S. Lebedeva, PhD<sup>111</sup>, Elisabeth Leehr, PhD<sup>28</sup>, Sara Lera-Miguel, PhD<sup>112</sup>, Klaus-Peter Lesch, MD<sup>113</sup>, Christine Lochner, PhD<sup>114</sup>, Mario R. Louza, MD, PhD<sup>115</sup>, Beatriz Luna, PhD<sup>99</sup>, Astri J. Lundervold, PhD<sup>116</sup>, Frank P. MacMaster, PhD<sup>117</sup>, Luigi A. Maglanoc, PhD<sup>118</sup>, Charles B. Malpas, PhD<sup>119</sup>, Maria J. Portella, PhD<sup>120</sup>, Rachel Marsh, PhD<sup>121</sup>, Fiona M. Martyn, BSc<sup>43</sup>, David Mataix-Cols, PhD<sup>122</sup>, Daniel H. Mathalon, PhD, MD<sup>123</sup>, Hazel McCarthy, PhD<sup>68</sup>, Colm McDonald, PhD<sup>43</sup>, Genevieve McPhilemey, PhD<sup>43</sup>, Susanne Meinert, MSc<sup>28</sup>, José M. Menchón, MD, PhD<sup>124</sup>, Luciano Minuzzi, MD, PhD<sup>125</sup>, Philip B. Mitchell, MBBS, MD<sup>44</sup>, Carmen Moreno, MD, PhD<sup>17</sup>, Pedro Morgado, MD, PhD<sup>126</sup>, Filippo Muratori, MD<sup>40</sup>, Clodagh M. Murphy, MD, PhD<sup>127</sup>, Declan Murphy, MD<sup>128</sup>, Benson Mwangi, PhD<sup>129</sup>, Leila Nabulsi, PhD<sup>43</sup>, Akiko Nakagawa, MD, PhD<sup>90</sup>, Takashi Nakamae, MD, PhD<sup>7</sup>, Leyla Namazova, MD, PhD<sup>26</sup>, Janardhanan Narayanaswamy, MD<sup>130</sup>, Neda Jahanshad, PhD<sup>5</sup>, Danai D. Nguyen, PhD<sup>131</sup>, Rosa Nicolau, MSc<sup>132</sup>, Ruth L. O'Gorman Tuura, PhD<sup>133</sup>, Kirsten O'Hearn, PhD<sup>134</sup>, Jaap Oosterlaan, PhD<sup>135</sup>, Nils Opel, MD<sup>28</sup>, Roel A. Ophoff, PhD<sup>136</sup>, Bob Oranje, PhD<sup>137</sup>, Victor Ortiz-García de la Foz, BSc<sup>138</sup>, Bronwyn J. Overs, BPsych(Hons)<sup>139</sup>, Yannis Paloyelis, PhD<sup>140</sup>, Christos Pantelis, MD, FRCPsych<sup>141</sup>, Mara Parellada, MD, PhD<sup>17</sup>, Paul Pauli, PhD<sup>142</sup>, Maria Picó-Pérez, PhD<sup>126</sup>, Felipe A. Picon, PhD<sup>77</sup>, Fabrizio Piras, PhD<sup>20</sup>, Federica Piras, PhD<sup>20</sup>,

Kerstin J. Plessen, MD, PhD<sup>143</sup>, Edith Pomarol-Clotet, MD, PhD<sup>13</sup>, Adrian Preda, MD<sup>144</sup>, Olga Puig, PhD<sup>42</sup>, Yann Quidé, PhD<sup>44</sup>, Joaquim Radua, MD, PhD<sup>34</sup>, J. Antoni Ramos-Quiroga, MD, PhD<sup>145</sup>, Paul E. Rasser, MSc<sup>146</sup>, Lisa Rauer, MSc<sup>79</sup>, Janardhan Reddy, MD<sup>130</sup>, Ronny Redlich, PhD<sup>28</sup>, Andreas Reif, MD<sup>147</sup>, Liesbeth Reneman, MD, PhD<sup>148</sup>, Jonathan Repple, MD<sup>28</sup>, Alessandra Retico, PhD<sup>149</sup>, Vanesa Richarte, MD<sup>145</sup>, Anja Richter, PhD<sup>79</sup>, Pedro GP. Rosa, MD<sup>39</sup>, Katya K. Rubia, PhD<sup>150</sup>, Ryota Hashimoto, MD, PhD<sup>151</sup>, Matthew D. Sacchet, PhD<sup>152</sup>, Raymond Salvador, PhD<sup>13</sup>, Javier Santonja, MSc<sup>153</sup>, Kelvin Sarink, BSc<sup>28</sup>, Salvador Sarró, MD, PhD<sup>13</sup>, Theodore D. Satterthwaite, MD<sup>81</sup>, Akira Sawa, MD, PhD<sup>45</sup>, Ulrich Schall, MD, PhD, DSc<sup>146</sup>, Peter R. Schofield, PhD, DSc<sup>154</sup>, Anouk Schranter, PhD<sup>148</sup>, Jochen Seitz, MD<sup>155</sup>, Mauricio H. Serpa, MD, PhD<sup>39</sup>, Esther Setién-Suero, PhD<sup>22</sup>, Philip Shaw, PhD<sup>156</sup>, Devon Shook, PhD<sup>137</sup>, Tim J. Silk, PhD<sup>157</sup>, Kang Sim, MD<sup>158</sup>, Schmitt Simon, MSc<sup>98</sup>, Helen Blair Simpson, MD, PhD<sup>159</sup>, Aditya Singh, MS<sup>61</sup>, Antonin Skoch, MD, PhD<sup>95</sup>, Norbert Skokauskas, MD, PhD<sup>160</sup>, Jair C. Soares, MD, PhD<sup>129</sup>, Noam Soreni, MD<sup>161</sup>, Carles Soriano-Mas, PhD<sup>124</sup>, Gianfranco Spalletta, MD, PhD<sup>20</sup>, Filip Spaniel, MD, PhD<sup>95</sup>, Stephen M. Lawrie, MD<sup>16</sup>, Emily R. Stern, PhD<sup>162</sup>, S. Evelyn Stewart, MD<sup>101</sup>, Yoichiro Takayanagi, MD, PhD<sup>163</sup>, Henk S. Temmingh, MD, PhD<sup>78</sup>, David F. Tolin, PhD<sup>164</sup>, David Tomecek, MSc<sup>95</sup>, Diana Tordesillas-Gutiérrez, PhD<sup>138</sup>, Michela Tosetti, PhD<sup>165</sup>, Anne Uhlmann, PhD<sup>78</sup>, Therese van Amelsvoort, MD, PhD<sup>166</sup>, Nic JA. van der Wee, MD, PhD<sup>167</sup>, Steven JA. van der Werff, PhD<sup>167</sup>, Neeltje EM. van Haren, PhD<sup>168</sup>, Guido A. van Wingen, PhD<sup>169</sup>, Alasdair Vance, MD, PhD<sup>170</sup>, Javier Vázquez-Bourgon, MD, PhD<sup>22</sup>, Daniela Vecchio, PhD<sup>20</sup>, Ganesan Venkatasubramanian, MD, PhD<sup>130</sup>, Eduard Vieta, MD, PhD<sup>34</sup>, Oscar Vilarroya, MD, PhD<sup>171</sup>, Yolanda Vives-Gilabert, PhD<sup>172</sup>, Aristotle N. Voineskos, MD, PhD<sup>57</sup>, Henry Völzke, MD<sup>173</sup>, Georg G. von Polier, MD<sup>174</sup>, Esther Walton, PhD<sup>175</sup>, Thomas W. Weickert, PhD<sup>37</sup>, Cynthia Shannon Weickert, PhD<sup>37</sup>, Andrea S. Weideman, MBA<sup>176</sup>, Katharina Wittfeld, PhD<sup>177</sup>, Daniel H. Wolf, MD, PhD<sup>81</sup>, Mon-Ju Wu, PhD<sup>129</sup>, Tony T. Yang, MD, PhD<sup>178</sup>, Kun Yang, PhD<sup>45</sup>, Yuliya Yoncheva, PhD<sup>179</sup>, Je-Yeon Yun, MD, PhD<sup>180</sup>, Yuqi Cheng, PhD<sup>181</sup>, Marcus V. Zanetti, MD, PhD<sup>39</sup>, Georg C. Ziegler, MD<sup>113</sup>, Barbara Franke, PhD<sup>182</sup>, Martine Hoogman, PhD<sup>183</sup>, Jan K. Buitelaar, MD, PhD<sup>184</sup>, Daan van Rooij, PhD<sup>185</sup>, Ole A. Andreassen, MD, PhD<sup>186</sup>, Christopher RK. Ching, PhD<sup>5</sup>, Dick J. Veltman, MD, PhD<sup>187</sup>, Lianne Schmaal, PhD<sup>6</sup>, Dan J. Stein, MD, PhD<sup>188</sup>, Odile A. van den Heuvel, MD, PhD<sup>32</sup>, Jessica A. Turner, PhD<sup>189</sup>, Theo GM. van Erp, PhD<sup>176</sup>, Zdenka Pausova, MD<sup>3</sup>, Paul M. Thompson, PhD<sup>5</sup>, and Tomas Paus, MD, PhD<sup>2</sup>

**Corresponding Author:**

Tomas Paus  
 Bloorview Research Institute  
 150 Kilgour Rd, East York, ON M4G 1R8  
[tpaus@hollandbloorview.ca](mailto:tpaus@hollandbloorview.ca)  
 Tel: (416) 425-6220, extension 6023

## Affiliations

1. Institute of Medical Science, University of Toronto, Toronto, ON, Canada
2. Bloorview Research Institute, Holland Bloorview Kids Rehabilitation Hospital, Toronto, ON, Canada
3. The Hospital for Sick Children, Toronto, ON, Canada
4. Krembil Centre for Neuroinformatics, Centre for Addiction and Mental Health, Toronto, ON, Canada
5. Imaging Genetics Center, Mark & Mary Stevens Neuroimaging & Informatics Institute, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA
6. Orygen, The National Centre of Excellence in Youth Mental Health, Parkville, Australia
7. Department of Psychiatry, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan
8. Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
9. Department of Psychiatry, Yale University
10. Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia, Canada
11. University of Groningen, University Medical Center Groningen, Department of Biomedical Sciences of Cells and Systems, Cognitive Neuroscience Center, Groningen, Netherlands
12. Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, IISGM, CIBERSAM, Spain
13. FIDMAG Germanes Hospitalàries Research Foundation, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Barcelona, Catalonia, Spain.
14. The Centre for Addiction and Mental Health, Campbell Family Mental Health Research Institute, University of Toronto, Toronto, Ontario, Canada
15. Department of Pediatrics University of Toronto, Ontario, Canada
16. Division of Psychiatry, University of Edinburgh, Royal Edinburgh Hospital, Edinburgh, Scotland, UK
17. Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, IISGM, School of Medicine, Universidad Complutense, CIBERSAM,
18. The Mathison Centre for Mental Health Research & Education, Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada
19. Social, Genetic and Developmental Psychiatry Centre; Institute of Psychiatry, Psychology and Neuroscience; King's College London, UK
20. Laboratory of Neuropsychiatry, IRCCS Santa Lucia Foundation, Rome, Italy
21. INT UMR 7289, Aix-Marseille Université, CNRS, France
22. Department of Psychiatry. Marqués de Valdecilla University Hospital, IDIVAL, School of Medicine, University of Cantabria; Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Santander, Spain
23. Department of Psychiatry and Neuropsychology, School of Mental Health and Neuroscience, Maastricht University, The Netherlands
24. Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Mannheim, Medical Faculty Mannheim / Heidelberg University, Mannheim, Germany
25. Department of Genetics, Instituto de Biociências, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil
26. The Research Institute of Pediatrics and Child Health of the Central Clinical Hospital of the Russian Academy of Sciences of the Ministry of Science and Higher Education of the Russian Federation, Russia
27. Magnetic Resonance Image Core Facility, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS). Barcelona, Spain
28. University of Münster, Department of Psychiatry
29. Turner Institute for Brain and Mental Health, School of Psychological Sciences, Monash University, Melbourne, Australia
30. Psychiatry and Clinical Psychobiology, Division of Neuroscience, Scientific Institute Ospedale San Raffaele, Milano, Italy
31. Department of Basic Medical Science, Neuroscience and Sense Organs, University of Bari 'Aldo Moro', Bari, Italy

32. Amsterdam UMC, Vrije Universiteit Amsterdam, Dept. of Psychiatry, Dept. of Anatomy & Neuroscience, Amsterdam Neuroscience, Amsterdam, Netherlands
33. Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, Department of Psychiatry, Utrecht, The Netherlands
34. Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Barcelona, Spain
35. Department of Psychiatry, University of Basel, Switzerland
36. McLean Hospital, Harvard Medical School, Belmont, MA, USA
37. School of Psychiatry, University of New South Wales, Sydney, NSW, Australia
38. Institute for diagnostic Radiology and Neuroradiology, University Medicine Greifswald, Germany
39. Laboratory of Psychiatric Neuroimaging (LIM-21), Departamento e Instituto de Psiquiatria, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo
40. Department of Developmental Neuroscience — IRCCS Fondazione Stella Maris, Pisa, Italy
41. Tri-institutional Center for Translational Research in Neuroimaging and Data Science (TReNDS), Georgia State University, Georgia Institute of Technology, Emory University, Atlanta, GA, USA
42. Department of Child and Adolescent Psychiatry and Psychology. Hospital Clinic, Barcelona, 2017SGR881. CIBERSAM, Spain.
43. Centre for Neuroimaging & Cognitive Genomics (NICOG), Clinical Neuroimaging Laboratory, NCBES Galway Neuroscience Centre, College of Medicine Nursing and Health Sciences, National University of Ireland Galway, H91 TK33 Galway, Ireland
44. School of Psychiatry, University of New South Wales, Randwick NSW, Australia
45. Department of Psychiatry, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA.
46. Department of Neuroscience, Brighton and Sussex Medical School, University of Sussex, Brighton, UK
47. Centre for Integrative Neuroscience and Neurodynamics, School of Psychology and Clinical Language Sciences, University of Reading, Reading, UK
48. Departments of Paediatrics and Psychiatry, University of Melbourne, Australia
49. Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital of Tübingen, Germany
50. Department of Psychiatry. Marqués de Valdecilla University Hospital, IDIVAL, School of Medicine, University of Cantabria; Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Santander, Spain; Hospital Universitario Virgen del Rocío, Sevilla, Spain; Departamento de Psiquiatria, Universidad de Sevilla, Instituto de Biomedicina de Sevilla (IBIS), Spain
51. Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, De Crespigny Park, London UK; Zurich Center for Neuroeconomics, University of Zurich, Switzerland
52. Department of Psychiatry and Behavioral Sciences, University of Minnesota, Minneapolis, Minnesota, USA
53. Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology, & Neuroscience, King's College London, Sackler Institute for Translational Neurodevelopment, London, United Kingdom
54. Orygen, Melbourne, Australia
55. Department of Psychiatry, Amsterdam UMC, location AMC, Netherlands
56. IRCCS Casa Solievo della Sofferenza, San Giovanni Rotondo, Italy
57. Campbell Family Mental Health Institute, Centre for Addiction and Mental Health, University of Toronto, Canada
58. Department of Psychology, School of Arts and Social Sciences, City, University of London, Northampton Square, Clerkenwell, London EC1V 0HB, United Kingdom
59. Division of Psychological and Social Medicine and Developmental Neurosciences, Faculty of Medicine, TU Dresden, Germany
60. Department of Psychiatry and Biological Sciences, Albert Einstein College of Medicine, New York, USA
61. University Medical Center Goettingen, Department of Psychiatry and Psychotherapy, Systems Neuroscience and Imaging in Psychiatry, Göttingen, Germany

62. Department of Psychiatry, University of Tuebingen, Germany
63. Behavioral Neuroscience Department, Oregon Health & Science University, USA
64. Departments of Psychiatry and of Neuroscience and Physiology, SUNY Upstate Medical University, Syracuse, NY, USA
65. Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA
66. Child OCD and Anxiety Disorders Program, Department of Psychiatry, University of Michigan Medical School, USA
67. San Francisco VA Medical Center, San Francisco, CA 94121, USA
68. Department of Psychiatry, Trinity College Dublin, Ireland
69. University of East London, School of Psychology, London, UK
70. Neuroscience Research Australia (NeuRA), Sydney, NSW, Australia
71. Department of Neuroscience, Brighton and Sussex Medical School, Brighton, UK
72. Tommy Fuss Center for Neuropsychiatric Disease Research, Department of Psychiatry, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA
73. School of Psychiatry, University of New South Wales, Randwick NSW, Australia
74. Central Clinical Hospital of the Russian Academy Sciences, Moscow, Russia
75. Department of Psychology, Stanford University, Stanford, CA, USA
76. Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Greifswald, Germany
77. Department of Psychiatry, Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil
78. Department of Psychiatry and Mental Health, University of Cape Town, Australia
79. Section for Experimental Psychopathology and Neuroimaging, Department of General Psychiatry, Heidelberg University Hospital, Heidelberg, Germany
80. FIDMAG Germanes Hospitalàries Research Foundation, Spain
81. Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
82. Department of Bioengineering, Imperial College London, London, UK
83. Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
84. Department of Biomedicine, University of Bergen, Norway
85. Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne and Melbourne Health, Victoria, Australia
86. University of Groningen, University Medical Center Groningen, Department of Psychiatry, Interdisciplinary Center Psychopathology and Emotion regulation (ICPE), Groningen, The Netherlands
87. Department of Experimental Psychology, Vrije Universiteit, Amsterdam, Netherlands
88. Genentech, Inc., South San Francisco, CA, USA
89. Department of Psychology, University of Oslo, Norway
90. Research Center for Child Mental Development, Chiba University, Chiba, Japan
91. Department of Psychiatry and Weill Institute for Neurosciences, University of California, San Francisco, San Francisco, CA, USA
92. University of Groningen, University Medical Center Groningen, Department of Child and Adolescent Psychiatry, Netherlands
93. Radboud University Medical Center, Karakter University Center of child and adolescent psychiatry, Netherlands
94. Department of Psychiatry, Maryland Psychiatric Research Center, University of Maryland School of Medicine, Baltimore, MD, USA
95. National Institute of Mental Health, Klecany, Czech Republic
96. Department of Clinical Medicine, University of Bergen, Bergen, Norway
97. Neuroscience Institute, University of Cape Town, Australia
98. Dept. of Psychiatry and Psychotherapy, Philipps University Marburg, Marburg, Germany
99. Department of Psychiatry, University of Pittsburgh, USA
100. University of Oxford, UK
101. Department of Psychiatry, University of British Columbia, Vancouver, BC, Canada
102. Department of Internal Medicine, First Affiliated Hospital of Kunming Medical University, China

103. Research Institute of Pediatrics and child health of the Central clinical hospital of the Ministry of science and education, Moscow, Russia
104. Department of Psychiatry, Philipps-University Marburg, Marburg, Germany
105. Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada
106. Department of Neuroradiology, Klinikum rechts der Isar, Technische Universität München
107. Child Neuropsychology Section, Department of Child and Adolescent Psychiatry, Psychosomatics, and Psychotherapy, University Hospital RWTH Aachen, Aachen, Germany
108. Child Neuropsychology Section, University Hospital RWTH Aachen, German; JARA-Brain Institute II Molecular Neuroscience and Neuroimaging, Research Centre Juelich, Germany
109. Department of Psychiatry, Seoul National University College of Medicine, Seoul, Korea
110. Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
111. Mental health research Center, Moscow, Russia
112. Department of Child and Adolescent Psychiatry and Psychology, Hospital Clinic, Barcelona, Spain
113. Division of Molecular Psychiatry, Center of Mental Health, University of Würzburg, Würzburg, Germany
114. SA MRC Unit on Risk and Resilience in Mental Disorders, Department of Psychiatry, Stellenbosch University, South Africa
115. Institute of Psychiatry, University of Sao Paulo, Brazil
116. Department of Biological and Medical psychology, University of Bergen, Bergen, Norway
117. Departments of Psychiatry and Pediatrics, University of Calgary, Canada
118. University Centre for Information Technology, University of Oslo, Norway
119. Developmental Imaging, Murdoch Children's Research Institute, Melbourne, Australia
120. Group of Research in Mental Health, Institut d'Investigació Biomèdica Sant Pau, IIBSant Pau; Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Barcelona, Spain
121. Department of Psychiatry, Vagelos College of Physicians and Surgeons, Columbia University
122. Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
123. Department of Psychiatry and Weill Institute for Neurosciences, University of California, San Francisco, USA
124. Department of Psychiatry, Bellvitge University Hospital, Bellvitge Biomedical Research Institute-IDIBELL; Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Barcelona, Spain
125. McMaster University, Mood Disorders Program, SJH Hamilton, Ontario, Canada
126. Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal.
127. Department of Forensic and Neurodevelopmental Science, King's College London, London, United Kingdom
128. Dept of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry Psychology and Neuroscience, King's College, London
129. Louis A. Faillace, MD, Department of Psychiatry and Behavioral Sciences, The University of Texas Health Science Center at Houston
130. OCD clinic, Department of Psychiatry, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India
131. Department of Pediatrics, University of California, Irvine, USA
132. Department of Child and Adolescent Psychiatry and Psychology, Hospital Clinic, Barcelona.
133. Center for MR Research, University Children's Hospital, Zürich, Switzerland
134. Department of Physiology and Pharmacology, Wake Forest School of Medicine, Winston-Salem, NC, USA
135. Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Emma Neuroscience Group, department of Pediatrics, Amsterdam Reproduction & Development, Amsterdam, The Netherlands
136. Center for Neurobehavioral Genetics, University of California Los Angeles, Los Angeles, CA, USA
137. Department of Psychiatry, University Medical Center Utrecht, Utrecht University, the Netherlands

138. Neuroimaging Unit, Technological Facilities, Valdecilla Biomedical Research Institute IDIVAL; Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Santander, Spain
139. Neuroscience Research Australia, Sydney, Australia
140. Department of Neuroimaging, Institute of Psychiatry, Psychology and Neuroscience, King's College London, De Crespigny Park, London SE5 8AF, UK
141. Melbourne Neuropsychiatry Centre, University of Melbourne
142. Department of Psychology (Biological Psychology, Clinical Psychology, and Psychotherapy), and Center of Mental Health, University of Würzburg, Würzburg, Germany
143. Division of Child and Adolescent Psychiatry, Department of Psychiatry, Lausanne University Hospital, Lausanne, Switzerland; Child and Adolescent Mental Health Center, Mental Health Services, Capital Region of Denmark, Denmark
144. Department of Psychiatry and Human Behavior, University of California, Irvine, USA
145. Department of Psychiatry, Hospital Universitari Vall d'Hebron, Barcelona, Catalonia, Spain. Group of Psychiatry, Mental Health and Addictions, Vall d'Hebron Research Institute, Barcelona, Catalonia, Spain. Department of Psychiatry and Forensic Medicine, Universitat Autònoma de Barcelona, Barcelona, Catalonia, Spain.
146. Priority Centre for Brain & Mental Health Research, The University of Newcastle, Callaghan NSW, Australia
147. Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt, Germany
148. Department of Radiology and Nuclear Medicine, Amsterdam University Medical Centers, University of Amsterdam, the Netherlands
149. National Institute for Nuclear Physics, Pisa Division, Pisa, Italy
150. Department of Child & Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
151. Department of Pathology of Mental Diseases, National Institute of Mental Health, National Center of Neurology and Psychiatry, Japan
152. Center for Depression, Anxiety, and Stress Research, McLean Hospital, Harvard Medical School, Belmont, MA, USA
153. Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, IISGM, Facultad de Psicología, Universidad Autónoma de Madrid
154. Neuroscience Research Australia, Sydney, NSW, Australia
155. Department of Child and Adolescent Psychiatry, RWTH Aachen University Hospital, Aachen
156. National Human Genome Research Institute and National Institute of Mental Health, Bethesda, MD, USA
157. School of Psychology, Deakin University, Geelong, Melbourne, Australia
158. West Region, Institute of Mental Health, Singapore
159. Columbia University Irving Medical Center, USA
160. Center for child and adolescent mental health, Institute of Mental Health, Norwegian University of Science and Technology
161. Pediatric OCD Consultation Clinic, Anxiety Treatment and Research Center, SJH Hamilton, Ontario, Canada
162. Department of Psychiatry, New York University School of Medicine, Nathan Kline Institute, New York, USA
163. Department of Neuropsychiatry, University of Toyama Graduate School of Medicine and Pharmaceutical Sciences, Toyama, Japan.
164. Anxiety Disorders Center, The Institute of Living
165. Laboratory of Medical Physics and Magnetic Resonance - IRCCS Fondazione Stella Maris, Pisa, Italy
166. Department of Psychiatry and Neuropsychology, Maastricht University, Maastricht, The Netherlands
167. Department of Psychiatry, Leiden University Medical Center, Leiden, the Netherlands
168. Department of child and adolescent psychiatry/psychology, Erasmus University Medical Centre, Rotterdam Netherlands



169. Amsterdam UMC, University of Amsterdam, Department of Psychiatry, Amsterdam Neuroscience, Amsterdam, The Netherlands
170. Academic Child Psychiatry Unit, Department of Pediatrics, University of Melbourne, Royal Children's Hospital, Australia
171. Department of Psychiatry and Forensic Medicine, Autonomous University of Barcelona, Cerdanyola del Vallès, Spain
172. Instituto ITACA, Universitat Politècnica de València, Valencia, Spain
173. Institute for Community Medicine, University Medicine Greifswald, Germany
174. Department for Child- and Adolescent Psychiatry, University Hospital RWTH Aachen, Germany
175. Department of Psychology, University of Bath, UK
176. Clinical Translational Neuroscience Laboratory, University of California Irvine, Irvine, CA, USA; Center for the Neurobiology of Learning and Memory, University of California Irvine, Irvine, CA, USA
177. German Center for Neurodegenerative Diseases (DZNE), Rostock/Greifswald, Germany
178. University of California San Francisco (UCSF), Department of Psychiatry, Division of Child and Adolescent Psychiatry, UCSF Weill Institute for Neurosciences, San Francisco, California, 94143 USA.
179. Department of Child and Adolescent Psychiatry, NYU Child Study Center, Hassenfeld Children's Hospital at NYU Langone
180. Seoul National University Hospital, Seoul, Republic of Korea
181. Department of Psychiatry, First Affiliated Hospital of Kunming Medical University
182. Departments of Human Genetics and Psychiatry, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands
183. Department of Human Genetics, Radboud University Medical Center, Nijmegen, The Netherlands
184. Department of Cognitive Neuroscience, Donders Institute for Brain, Cognition and Behaviour, Radboudumc, Nijmegen, The Netherlands
185. Donders Centre for Cognitive Neuroimaging, Radboud University Medical Centre, Nijmegen, Netherlands
186. Norwegian Centre for Mental Disorders Research (NORMENT), Institute of Clinical Medicine, University of Oslo, Oslo, Norway
187. Department of Psychiatry, Amsterdam UMC, location VUMC, Amsterdam, the Netherlands
188. SAMRC Unit on Risk & Resilience in Mental Disorders, Dept of Psychiatry and Neuroscience Institute, University of Cape Town
189. Psychology Department & Neuroscience Institute, Georgia State University, Atlanta, GA, USA

## Figure legend

Figure 1: Meta-analytic profiles of group differences in cortical thickness (left hemisphere only) between cases and controls across the six psychiatric disorders investigated. Group differences are adjusted for age, sex and other site-specific variables. Error bars represent 95% confidence intervals. Estimates below zero represent thinner cortex in cases as compared with controls.

Figure 2 A. Cross disorder correlation of group differences in cortical thickness (profiles from Figure 1). B). Cross disorder genetic correlation (LD score regression) derived from Brainstorm et al. *Science* 2018. C. Plot of genetic correlation against phenotypic (MRI-derived difference in thickness) correlations between psychiatric disorders with a linear model fit (blue line,  $R^2=0.27$ , Mantels p value = 0.034, Pearson p value < 0.05). \* FDR-pvalue < 0.05, \*\* < 0.01, \*\*\* < 0.001.

Figure 3. Results from virtual histology. Distribution of correlation coefficients between cell-specific gene expression profiles and group differences in cortical thickness for the six psychiatric disorders. \*represents FDR p < 0.05.

Figure 4. Principal components analysis of profiles of group differences across six psychiatric disorders. A. First principal component, PC1, plotted across the 34 regions of the left hemisphere. PC1 values are scaled down to have a max of zero in order to facilitate interpretation: negative values reflect greater differences in cortical thickness between cases and controls. Unscaled values presented in eFigure 3. B. Distribution of correlation coefficients between cell specific gene expression and PC1 profile. \* indicates FDR-p-value < 0.05.

Figure 5. Lifespan trajectory in gene expression of PC1-CA1 co-expressed genes. Each line represents a fitted loess model for the expression of a given gene. Genes and their fitted models are coloured based on clustering based on temporal trajectories. PC1-CA1 co-expressed genes were generated using co-expression of seed genes, namely genes that correlate with PC1 profile and the 103 CA1 pyramidal specific genes passing FDR < 0.05. Gene ontology (GO) enrichment analysis of the prenatal cluster (B), and postnatal cluster (C).

## Figure titles

Figure 1: Meta-analytic profiles of group differences in cortical thickness (left hemisphere only) between cases and controls

Figure 2: Phenotypic and genetic similarity between psychiatric disorders

Figure 3: Virtual histology correlations between psychiatric group differences in thickness and cell specific gene expression

Figure 4: Principal component 1 from the six psychiatric disorder profiles

Figure 5: Psychiatric disorder implicated PC1-CA1 Pyramidal gene co-expression and enrichment analysis